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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/120,044 07/21/98 MINETTI

C 1758-4036US2

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NEW YORK NY 10154

HM22/1109

EXAMINER

DEVI, S

ART UNIT	PAPER NUMBER
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1641

DATE MAILED:

11/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Applicant(s)	Minetti et al.
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Group Art Unit
1641



- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Part of Paper No. 13

DETAILED ACTION

Priority

- 1) The instant application claims domestic priority under 35 U.S.C. 119(e) to two non-provisional applications, SN 60/053,306 filed 07/21/97 and SN 60/073,456 filed 02/02/98.

Preliminary Amendment

- 2) Acknowledgment is made of Applicants' preliminary amendment filed 08/31/98 (paper no. 6).
- 6). With this, Applicants have amended the specification.

Election

- 3) Acknowledgment is made of Applicants' election, filed 08/5/99 (paper no. 12), of invention I, claims 1-15 and 22-26, and of the pneumolysin species, pNV207 (claim 13), in response to the restriction requirement mailed 08/04/99 (paper no. 10). Applicants have not traversed the restriction requirement. However, Applicants request the Office to reconsider the restriction of inventions I, III and IV, since they are related as product and process of use of the product.

Applicants are asked to note that claims 27-29 will be retained as pending claims pursuant to the rejoinder provisions of M.P.E.P 821.04 and will be withdrawn from consideration until such time as the subject matter of claims 1-15 and 22-26 are deemed allowable. The Examiner in charge of the instant application will then determine if claims 27-29 include all of the limitations of the allowable product claims prior to determining if rejoinder will be permitted under M.P.E.P 821.04.

Applicants are asked to note that the Office has examined all the modified pneumolysin species recited in claims 7, 12, 14 and 15, since the elected modified pneumolysin species, pNV207, is found to be free of prior art currently of record.

Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement set forth for inventions II and V, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)). The Examiner maintains the restriction requirement set forth in paper no. 5. This restriction requirement is therefore made FINAL.

Status of Claims

- 4) Claims 4 and 17 have been amended via paper no. 6 filed 08/31/98.

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Claims 1-30 are pending in this application.

Claims 16-21 and 27-30 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. § 821.03. Claims 8-11 are also withdrawn from further consideration since they are drawn to non-elected species.

Claims 1-7, 12-15 and 22-26 are under examination. An Action on the Merits for these claims is issued.

Information Disclosure Statements

5) Acknowledgment is made of Applicants' Information Disclosure Statements filed 02/03/99 and 05/11/99 (paper no. 8 and 11). The information referred to therein has been considered and signed copies of the same are attached to this Office Action (paper no. 13).

Sequence Listing

6) Acknowledgment is made of Applicants' submission of a raw sequence listing and a computer readable copy of the same on 08/31/98 (paper no. 3), which have been entered in the case.

Drawings

7) This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification/Informalities

8) The specification of the instant application is objected to for the following reasons:

(a) Figure 14 is confusing in the designations: PLYD mutant A and PLYD mutant B. These mutants do not appear to be described elsewhere, and it is unclear as to what amino acid substitutions they carry.

(b) The drawings 1-4 are objected to by the Examiner for improper labeling of subparts. The sequences of Figure 1, 2, 3 and 4 flow into the next pages. The first page of each drawing should be labeled as Figure 1A, 2A, 3A and 4A, and the second continuing page as Figure 1B, 2B, 3B and 4B. The figure descriptions on page 8 of the specification should refer to these sections as 1A and 1B, 2A and 2B, 3A and 3B and 4A and 4B respectively. References to these Figures throughout the specification should be amended accordingly.

Rejection(s) - 35 U.S.C. § 112, First Paragraph

9) Claims 1-3 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a refoldable, modified, hemolytically attenuated, pneumolysin polypeptide as obtained by specifically mutating the nucleic acid molecule encoding a wild-type pneumolysin at one position, such as, 207, 103, 111 or 211, does not reasonably provide enablement for a modified or attenuated pneumolysin polypeptide obtained by a mutation at any one random position, or more than one positions as, claimed in a broad sense.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention includes modifying or attenuating a wild-type pneumolysin polypeptide by random mutation of the nucleic acid molecule, which encodes a wild type pneumolysin. Although the relative skill of those in this art is high, the breadth of the claims encompasses any refoldable, modified, hemolytically attenuated, pneumolysin polypeptide obtained by mutation of a nucleic acid molecule encoding a wild type pneumolysin at **any** random position or positions, or the one wherein "at least one amino acid in the region comprising amino acid residues 1 to 257 is substituted" as recited in claim 2. Refoldable, modified or attenuated pneumolysin polypeptides having more than random mutations at any positions are also encompassed in the scope of instant claims. However, a review of instant disclosure suggests that the entire scope of the claims is not enabled. The circular dichroism data in the specification, as disclosed on page 76 and Figure 16A, show that the mutant, pNV207, is enabled as a refoldable, attenuated pneumolysin. The evidence in the specification, as disclosed on page 62, Tables 4 and 9, is enabling for additional refoldable, attenuated pneumolysin mutants having a single residue

mutation, i.e., pNV111, pNV211 and pNV103, because these mutants have been shown to be immunogenic, capable of producing antibodies that neutralize the wild-type pneumolysin.

The specification itself discloses that even with a substitution at a single amino acid position (let alone combination of substitutions), the refoldability of the resultant single mutant polypeptide is an unpredictable event. For instance, the specification discloses that single mutations at positions 243, 286 and 446 of the wild-type pneumolysin, or a combination of substitutions at positions 243 and 446, resulted in insoluble inclusion bodies, and attempted refolding of these mutants yielded aggregate species (see pages 57, 58 and Table 5B). Obviously, such insoluble and non-refoldable or non-functional pneumolysins would lack the structural, functional and immunological and/or biological integrity, and therefore, are not ideal protein carriers for preparation of polysaccharide conjugates of claims 22-26. Furthermore, there is no evidentiary support in the specification that a mutant with more than one mutation, if constructed, would be hemolytically attenuated and immunogenically functional, either as such, or as a conjugate in covalent association with a polysaccharide, as claimed in claims 22-26. It should be noted that modifications of a native polypeptide at multiple positions can potentially alter its conformational, antigenic and immunogenic integrity, and the use of such an excessively modified polypeptide as a protein carrier would potentially result in a non-effective conjugate vaccine. There is no evidence within the instant disclosure that such a modified pneumolysin would function effectively either in a conjugate or in a non-conjugate form. Thus, while the specification is enabling for the specifically disclosed single mutants, pNV207, pNV111, pNV211 and pNV103, it is not enabling for any of the myriad of modified pneumolysins currently encompassed in the scope of instant claims. The breadth of instant claims is not commensurate in scope with the enabling disclosure or evidence and clearly, one skilled in the art cannot make and use the invention as commensurate in scope with the claims without undue experimentation.

Similarly, it has been shown in the art that attenuation of the hemolytic activity of a wild-type pneumolysin by any random mutation is unpredictable. The state of the art on the attenuation of a pneumolysin polypeptide is still in development and reflects a high degree of unpredictability. For instance, Feldman *et al.* (*Am. J. Respir. Cell Mol. Biol.* 5: 416-423, 1991) show that, while a Trp 433 > Phe modification results in a modified pneumolysin having a

lowered haemolytic activity, a Tyr 384 > Phe modification results in a modified pneumolysin that had normal hemolytic activity (see page 417). The state of the art clearly suggests that a mutation at any random position does not result in a modified pneumolysin polypeptide with an attenuated hemolytic activity. Mitchell *et al.* (*Mol. Microbiol.* 5: 1883-1888, 1991) show that individual modifications of Trp 379 and Trp 397 to Phe, or of residues Tyr 384 and Asp 385 to Phe and Asn respectively, did not alter the cytolytic activities of resultant modified pneumolysins (see page 1885, left column). The state of the art at the time Applicants filed one of their provisional applications, SN 60/073,456, shows that an Asp 385 > Asn mutation in the pneumolysin gene resulted in a modified pneumolysin that retained 100% hemolytic activity of wild-type pneumolysin (see Table 1 of Alexander *et al. Microb. Pathogen.* 24: 167-174, March 1998). Applicants themselves acknowledge on page 26, lines 6-9, that several positions that fall in the range of amino acid residues 1-57 "are not associated with decreases in hemolytic activity".

As recited currently in a broad sense, a myriad of random mutations of the wild-type pneumolysin nucleic acid is encompassed in the scope of the claim and is required to reproducibly practice the full scope of instant claims. However, in light of the demonstrated unpredictability of obtaining an attenuated pneumolysin by any random mutation and in light of Applicants' own evidence showing that refoldable property even of a single mutant of pneumolysin is an unpredictable event, and the lack of or inadequate specific guidance and direction provided in the instant disclosure as to how to reproducibly obtain attenuated refoldable pneumolysins by random mutation(s) anywhere on the nucleic acid molecule of wild-type pneumolysins, or at any position in a region comprising amino acid residues 1 to 257 of type 14 pneumolysin, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed. Therefore, instant claims are viewed as non-enabling with respect to their full scope, and as not meeting the enablement provision of 35 U.S.C. § 112, first paragraph.

10) Claims 4-7 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4-6 encompass a modified pneumolysin polypeptide comprising at least one amino acid substitution in SEQ ID NO: 3 at position 61, 148 or 195, or a combination of substitutions at positions 33, 46, 83, 39 and 257 with the recited amino acid(s). However, no evidence exists within the instant specification that such modified pneumolysins, if produced, would be hemolytically attenuated and properly refolded as recited in base claim 2. The passage on page 24, lines 8 and 9, that "substitutions at one, or more, of positions 61, 148 and 195 **may** result in polypeptides having reduced hemolytic activity" (Emphasis added) is merely a simple guess which is not based on a concrete evidentiary support. There is no showing that any of the recited multiple substitutions indeed result in refoldable products. The state of the art as discussed above under paragraph 9 suggests that even a single substitution at any position does not always result in a hemolytically attenuated modified pneumolysins, let alone refoldable modified pneumolysins. Because of this art-recognized unpredictability factor, the modified pneumolysin polypeptides recited in claims 4-6 are viewed as being non-enabled.

Claim 7 is directed to a modified pneumolysin polypeptide, pNVJ1, which according to Table 5A, has five amino acid substitutions. However, no evidence is of record that establishes its refoldability. The likelihood of disruption of the secondary structure of a modified pneumolysin or a pneumolysoid, potentially resulting in an altered or lack of antigenicity is high, since the state of art reflects the caution taken by those skilled in the art in designing amino acid substitutions in a pneumolysin that are conservative in order to preserve its immunogenic functions. See page 2301, right column of Paton *et al.* (*Infect. Immun.* 59: 2297-2304, 1991 - Applicants' IDS). There is no showing within the instant specification that pNVJ1, carrying multiple amino acid substitutions, is operable or functional, and that it retains the conformational assembly required for its immunogenic functions, and that it brings about the effects that are desired for.

Clearly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application, to reproducibly practice the invention as claimed due to the lack of specific guidance and direction, the lack of working examples and lack of evidence enabling hemolytically attenuated, yet functional modified pneumolysins by the recited single or multiple amino acid substitution(s), the demonstrated unpredictability as reflected in the state of the art, and the quantity of experimentation necessary.

Rejections - 35 U.S.C. § 112, Second Paragraph

- 11)** The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

- 12)** Claims 1-6 and 22-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 2 is confusing, because it includes a sequence that is not identified by a SEQ ID number. As required under 37 C.F.R. 1.821(d), it is suggested that Applicants identify the sequence recited in claim 2, by providing the SEQ ID NO: ?? in parenthesis after the recitation "1 to 257". This is particularly important given the art-recognized variations in the numerical designation of amino acid residues in the sequence of a given polypeptide. While some skilled in the art number the amino acid residues starting from methionine (Met) at position 1, others in the art number the same polypeptide differently starting from an amino acid that is not methionine. See Figure 2 of Rossjohn *et al.* (*J. Mol. Biol.* 284: 449-461, 1998). Because of the diverse practice in the art of numbering amino acid residues of a polypeptide sequence, the recitation "amino acid residues 1 to 257" in the instant claims, without reciting the specific SEQ ID NO: becomes confusing.

(b) Claim 1 is confusing in the inconsistent recitation of "polypeptide" (see lines 1, 3, 10) and "polypeptides" (see lines 7 and 13), and "nucleic acid molecule" (see line 4) and "nucleic acid molecules" (see lines 6 and 9). Furthermore, the plural recitations lack proper antecedent basis.

(c) Claim 1 is vague and indefinite in the recitation "substantially", because it is unclear what is encompassed in this recitation, absent a definition.

(d) Claim 2 is vague and indefinite in the recitation "properly-refoldable", because it is unclear what is encompassed in this recitation, or what constitutes a "properly-refoldable" modified pneumolysin.

(e) Claims 22 and 25 are confusing in the recitation "a polysaccharide which elicits antibodies cross-reactive with a bacterial polysaccharide". Is the generically recited

"polysaccharide" (line 3) non-bacterial or non-microbial?

(f) Claims 23 and 26 are incorrect in the recitation "a bacteria selected from the group" (Emphasis added), because each of the Markush species recited is "a bacterium". It is suggested that Applicants change the recitation to --a bacterium-- in line 2 of the claims.

(g) Claim 23 is further confusing and/or incorrect in reciting "meningococcal group A, B or C" as a Markush bacterium species, because the recitation does not reflect the intended name of the bacterium. To obviate the rejection, it is suggested that Applicants replace the recitation with --meningococcus A, B or C--.

(h) Claim 24 lacks antecedence for the recitation "at least one pneumolysin... of claim 1", because claim 1 is not drawn to more than one pneumolysin, but only to "[a]" modified pneumolysin.

(i) Claim 26 is in an improper Markush format in the use of the word "or" while reciting the Markush species. The Office recommends the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing species.

(j) Claim 26 is vague and indefinite in the recitation, "the polysaccharide" (lines 1 and 2). Claim 26 depends from claim 25, which recites "a polysaccharide" and "a bacterial polysaccharide", and it is unclear which of these two polysaccharides of claim 25, "the polysaccharide" of claim 26 corresponds to. Clarification is required.

Rejection(s) - 35 U.S.C. § 102

13) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14) Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Lock *et al.* (*Microb. Pathogen.* 21: 71-83, 1996 - Applicants' IDS).

Lock *et al.* teach a modified pneumolysin, Ply8, having substantially reduced haemolytic activities compared to wild type pneumolysin, Ply, as tested by a haemolytic assay. Ply 8, produced by host cells, has a single amino acid substitution at position 172 (see abstract, and

pages 75 and 80). Purified Ply8 has a molecular weight of 54-55 kDa, which is "substantially similar" to the 53 kDa molecular weight of the wild type Ply (see pages 73 and 74). Lock *et al.* explicitly teach that antibodies "raised against Ply completely neutralize Ply8 haemolytic activity and *vice versa*" (see page 80) (Emphasis added). That antibodies are raised against Ply8, which neutralizes native Ply, clearly suggests that Lock's Ply8 is refoldable.

Claim 1 is anticipated by Lock *et al.*

15) Claims 1 and 22-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Paton *et al.* (*Infect. Immun.* 59: 2297-2304, 1991 - Applicants' IDS).

It is noted that Applicants use the terms, pneumolysoid and modified pneumolysin, interchangeably in the instant specification (see page 6, lines 8 and 9, for example).

Paton *et al.* teach modified pneumolysins or pneumolysoids or pneumolysin toxoids designated Pd-A and Pd-B. Pd-A carries a single mutation, i.e., a Cys->Gly amino acid substitution at position 428, whereas Pd-B carries a Trp->Phe substitution at position 433 (see abstract and page 2298, left column). The two pneumolysoids have a mobility corresponding to that of native or wild-type pneumolysin, i.e., a substantially similar molecular mass of 52 kDa, and show a reduced or attenuated hemolytic activity compared to that of native pneumolysin (see page 2299, right column, first paragraph under 'Results'). The pneumolysoids are produced by site-directed mutagenesis or single amino acid substitutions, which significantly reduce the hemolytic activity (see page 2298). The pneumolysoids are expressed by *E. coli* host cells and are assayed for hemolytic activity (see page 2298, right column, first paragraph). Both Pd-A and Pd-B contained in a pharmaceutically acceptable carrier such as PBS are taught (see page 2299, left column). Paton *et al.* teach the conjugation of Pd-B to the pneumococcal serotype 19F polysaccharide; a vaccine comprising the same is also taught (see page 2299, left column).

That Paton's Pd-B pneumolysoid (i.e., modified pneumolysin) having an attenuated haemolytic activity served as an effective immunogen, with and without conjugation to a polysaccharide, suggests that the single amino acid substitution at position 433 of a wild-type pneumolysin does not disrupt the secondary structure critical for the conformational and functional integrity of the modified pneumolysin. Thus, the limitation of refoldability is an inherent property of Paton's attenuated pneumolysin carrying a single amino acid substitution at

position 433.

The cross-reactivity of the capsular polysaccharide of pneumococcal serotype 19F with certain heterologous bacterial polysaccharides is an inherent property as is evident from the state of the art. For instance, Krishnamurthy *et al.* (*Infect. Immun.* 22: 727-735, 1978) teach that the capsular polysaccharide of serotype 19F pneumococcus is cross-reactive with the capsular polysaccharide of serotype 19A pneumococcus (see abstract). Similarly, Lee *et al.* (*J. Infect. Dis.* 151: 658-664, 1985) teach the cross-reactivity and structural similarities between the capsular polysaccharides of serotype 19F pneumococcus and *Klebsiella* K2 (see abstract).

Thus, the disclosure of Paton *et al.* anticipates the instant invention. The reference of Krishnamurthy *et al.* or Lee *et al.* is **not** used as a secondary reference in combination with Paton *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Paton *et al.*, because Krishnamurthy *et al.* or Lee *et al.* teach that the capsular polysaccharide of serotype 19F pneumococcus is cross-reactive with the capsular polysaccharide of a heterologous serotype of pneumococcus, or of a heterologous bacterium. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1 and 22-26 are anticipated by Paton *et al.*

Objections

16) Claims 3-6, 13, 23 and 26 are objected to for the following reasons.

(a) Claim 4 is objected to for the use of the confusing claim language. It is suggested that Applicants delete the recitation "SEQ ID NO: 3" at the end of the claim and insert it after "Formula I" in line 3. For clarity, proper reading and proper antecedent basis, and depending on whether Applicants intend an open or closed claim language, it is suggested that Applicants add the recitation --, said Formula I comprising--, or --, said Formula I consisting of" after the recitation "237 and 257" in line 6 of the claim.

(b) Claims 5 and 6 lack a comma after the recitation "lysine" in line 5.

(c) In line 4 of claim 6, the recitation "cystine" is misspelled.

(d) In line 3 of claim 23, the recitation "a" is unnecessary.

(e) Claims 23 and 26 are objected to for the inconsistent recitations: "streptococcus types" in claim 23 and "streptococcus serotypes" in claim 26. For consistency, it is suggested that

Applicants use either "types" or "serotypes", whichever is supported by the specification.

(f) Claim 23 is incorrect in the recitation "streptococcus types Ia, Ibor VIII and pneumococcal" (see last two lines) (Emphasis added). It is suggested that Applicants change the recitation to streptococcus type Ia, Ib or VIII and pneumococcus--.

(g) Claims 23 and 26 are objected to for inconsistent ways of reciting the bacteria, one by underlining and the other by italicizing: "Haemophilus influenzae" and "*S. pneumoniae*". For consistency, it is suggested that Applicants change the recitation "Haemophilus influenzae" to -- *Haemophilus influenzae*--.

(h) Claim 13 lacks a period at the end.

Relevant Prior Art

17) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Alexander *et al.* (*Infect. Immun.* 62: 5683-5688, 1994 - Applicants' IDS) teach immunization of mice with a pneumolysin toxoid to induce protective immunity against a range of (nine) serotypes of *Streptococcus pneumoniae*. Alexander *et al.* state that "[p]neumolysoid toxoids should be considered for inclusion in improved pneumococcal conjugate vaccine for use in humans" (see entire document).

- Lee *et al.* (*Vaccine* 12: 875-878, 1994) teach Pd-B pneumolysoid (i.e., pneumolysin with a Trp->Phe substitution at position 433) and its conjugation to serotype 19F pneumococcal polysaccharide. The conjugate conferred protection to infant mice born to pregnant or lactating mothers immunized with the conjugate (see entire publication).

- Hill *et al.* (*Infect. Immun.* 62: 757-758, 1994 - Applicants' IDS) teach mutant pneumolysins carrying amino acid substitutions at positions 31, 75, 127 and 156 (see entire publication).

- Berry *et al.* (*Infect. Immun.* 63: 1969-1974, 1995) teach multiple mutant pneumolysins with a reduced hemolytic activity (see entire publication).

Remarks

18) Claims 1-7 and 22-26 stand rejected.

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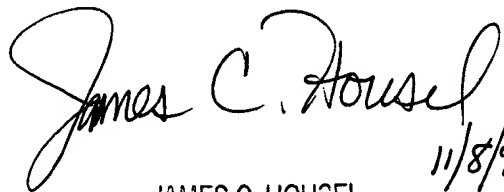
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- 19) Claims 12, 14 and 15 are free of prior art currently of record.
- 20) Claim 13 is free of prior art currently of record. However, the claim stands objected to.
- 21) Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.
- 22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

November 1999


JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER
11/8/99